AMIKACIN SULFATE- amikacin sulfate injection, solution
Teva Parenteral Medicines, Inc.

Amikacin Sulfate Injection USP

9032

9040

Rx only

To reduce the development of drug-resistant bacteria and maintain the effectiveness of amikacin sulfate injection USP and other antibacterial drugs, amikacin sulfate injection USP should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

WARNINGS

Patients treated with parenteral aminoglycosides should be under close clinical observation because of the potential ototoxicity and nephrotoxicity associated with their use. Safety for treatment periods which are longer than 14 days has not been established.

Neurotoxicity, manifested as vestibular and permanent bilateral auditory ototoxicity, can occur in patients with preexisting renal damage and in patients with normal renal function treated at higher doses and/or for periods longer than those recommended. The risk of aminoglycoside-induced ototoxicity is greater in patients with renal damage. High frequency deafness usually occurs first and can be detected only by audiometric testing. Vertigo may occur and may be evidence of vestibular injury. Other manifestations of neurotoxicity may include numbness, skin tingling, muscle twitching and convulsions. The risk of hearing loss due to aminoglycosides increases with the degree of exposure to either high peak or high trough serum concentrations. Patients developing cochlear damage may not have symptoms during therapy to warn them of developing eighth-nerve toxicity, and total or partial irreversible bilateral deafness may occur after the drug has been discontinued. Aminoglycoside-induced ototoxicity is usually irreversible.

Aminoglycosides are potentially nephrotoxic. The risk of nephrotoxicity is greater in patients with impaired renal function and in those who receive high doses or prolonged therapy.

Neuromuscular blockade and respiratory paralysis have been reported following parenteral injection, topical instillation (as in orthopedic and abdominal irrigation or in local treatment of empyema), and following oral use of aminoglycosides. The possibility of these phenomena should be considered if aminoglycosides are administered by any route, especially in patients receiving anesthetics; neuromuscular blocking agents such as tubocurarine, succinylcholine, decamethonium; or in patients receiving massive transfusions of citrate-anticoagulated blood. If blockage occurs, calcium salts may reverse these phenomena, but mechanical respiratory assistance may be necessary.

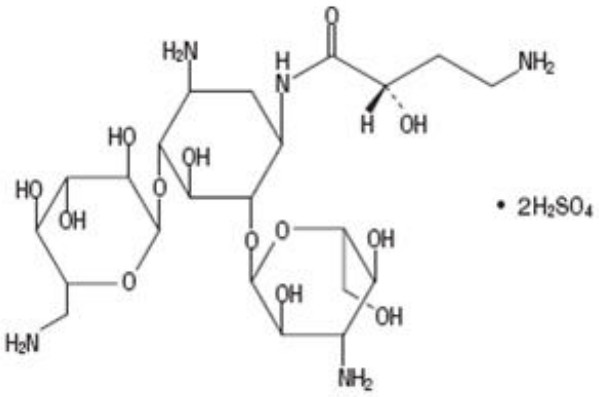
Renal and eighth-nerve function should be closely monitored especially in patients with known or suspected renal impairment at the onset of therapy and also in those whose renal function is initially normal but who develop signs of renal dysfunction during therapy. Serum concentrations of amikacin should be monitored when feasible to assure adequate levels and to avoid potentially toxic levels and prolonged peak concentrations above 35 micrograms per mL. Urine should be examined for decreased specific gravity, increased excretion of proteins and the presence of cells or casts. Blood urea nitrogen, serum creatinine or creatinine clearance should be measured periodically. Serial audiograms should be obtained where feasible in patients old enough to be tested, particularly high risk patients. Evidence of ototoxicity (dizziness, vertigo, tinnitus, roaring in the ears and hearing loss) or nephrotoxicity requires discontinuation of the drug or dosage adjustment.

Concurrent and/or sequential systemic, oral or topical use of other neurotoxic or nephrotoxic products, particularly bacitracin, cisplatin, amphotericin B, cephaloridine, paromomycin, viomycin, polymyxin B, colistin, vancomycin or other aminoglycosides should be avoided. Other factors that may increase risk of toxicity are advanced age and dehydration.

The concurrent use of amikacin with potent diuretics (ethacrynic acid or furosemide) should be avoided since diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue.

DESCRIPTION

Amikacin, USP (as the sulfate) is a semi-synthetic aminoglycoside antibiotic derived from kanamycin. D-Streptamine,*O*-3-amino-3-deoxy-α-D-glucopyranosyl-(1→6)-*O*-[6-amino-6-deoxy-α-D-glucopyranosyl-(1→4)]-N^1-(4-amino-2-hydroxy-1-oxobutyl)-2-deoxy-, (S)-, sulfate (1:2) (salt).



$C_{22}H_{43}N_5O_{13} \cdot 2H_2SO_4$ M.W. 781.75

Amikacin sulfate injection USP is supplied as a sterile, colorless to light straw-colored solution for intramuscular or intravenous use. The 500 mg per 2 mL vial and the 1 gram per 4 mL vial each contain, per mL, 250 mg amikacin, USP (as the sulfate), 2.5% sodium citrate dihydrate, 0.66% sodium metabisulfite, and water for injection, q.s. pH is adjusted with sulfuric acid and/or, if necessary, sodium hydroxide. The pH is 3.5 to 5.5.

CLINICAL PHARMACOLOGY

Intramuscular Administration

Amikacin is rapidly absorbed after intramuscular administration. In normal adult volunteers, average peak serum concentrations of about 12, 16 and 21 mcg/mL are obtained 1 hour after intramuscular administration of 250 mg (3.7 mg/kg), 375 mg (5 mg/kg), 500 mg (7.5 mg/kg), single doses, respectively. At 10 hours, serum levels are about 0.3 mcg/mL, 1.2 mcg/mL and 2.1 mcg/mL, respectively.

Tolerance studies in normal volunteers reveal that amikacin is well tolerated locally following repeated intramuscular dosing, and when given at maximally recommended doses, no ototoxicity or nephrotoxicity has been reported. There is no evidence of drug accumulation with repeated dosing for 10 days when administered according to recommended doses.

With normal renal function, about 91.9% of an intramuscular dose is excreted unchanged in the urine in the first 8 hours and 98.2% within 24 hours. Mean urine concentrations for 6 hours are 563 mcg/mL following a 250 mg dose, 697 mcg/mL following a 375 mg dose and 832 mcg/mL following a 500 mg dose.

Preliminary intramuscular studies in newborns of different weights (less than 1.5 kg, 1.5 to 2 kg, over 2 kg) at a dose of 7.5 mg/kg revealed that, like other aminoglycosides, serum half-life values were correlated inversely with post-natal age and renal clearances of amikacin. The volume of distribution indicates that amikacin, like other aminoglycosides, remains primarily in the extracellular fluid space of neonates. Repeated dosing every 12 hours in all the above groups did not demonstrate accumulation after 5 days.

Intravenous Administration

Single doses of 500 mg (7.5 mg/kg) administered to normal adults as an infusion over a period of 30 minutes produced a mean peak serum concentration of 38 mcg/mL at the end of the infusion and levels of 24 mcg/mL, 18 mcg/mL and 0.75 mcg/mL at 30 minutes, 1 hour and 10 hours post-infusion, respectively. Eighty-four percent of the administered dose was excreted in the urine in 9 hours and about 94% within 24 hours.

Repeat infusions of 7.5 mg/kg every 12 hours in normal adults were well tolerated and caused no drug accumulation.

General

Pharmacokinetic studies in normal adult subjects reveal the mean serum half-life to be slightly over 2 hours with a mean total apparent volume of distribution of 24 liters (28% of the body weight). By the ultrafiltration technique, reports of serum protein binding range from 0 to 11%. The mean serum clearance rate is about 100 mL/min and the renal clearance rate is 94 mL/min in subjects with normal renal function.

Amikacin is excreted primarily by glomerular filtration. Patients with impaired renal function or diminished glomerular filtration pressure excrete the drug much more slowly (effectively prolonging the serum half-life). Therefore, renal function should be monitored carefully and dosage adjusted accordingly (see suggested dosage schedule under **DOSAGE AND ADMINISTRATION**).

Following administration at the recommended dose, therapeutic levels are found in bone, heart, gallbladder, and lung tissue in addition to significant concentrations in urine, bile, sputum, bronchial secretions, interstitial, pleural, and synovial fluids.

Spinal fluid levels in normal infants are approximately 10 to 20% of the serum concentrations and may reach 50% when the meninges are inflamed. Amikacin has been demonstrated to cross the placental barrier and yield significant concentrations in amniotic fluid. The peak fetal serum concentration is about 16% of the peak maternal serum concentration and maternal and fetal serum half-life values are about 2 and 3.7 hours, respectively.

Microbiology

Mechanism of Action

Amikacin, an aminoglycoside, binds to the prokaryotic ribosome, inhibiting protein synthesis in susceptible bacteria. It is bactericidal *in vitro* against Gram-positive and Gram-negative bacteria.

Mechanism of Resistance

Aminoglycosides are known to be ineffective against *Salmonella* and *Shigella* species in patients. Therefore, *in vitro* susceptibility test results should not be reported.

Amikacin resists degradation by certain aminoglycoside inactivating enzymes known to affect gentamicin, tobramycin, and kanamycin.

Aminoglycosides in general have a low order of activity against Gram-positive organisms other than *Staphylococcal* isolates.

Interaction with Other Antimicrobials

In vitro studies have shown that amikacin sulfate combined with a beta-lactam antibiotic acts synergistically against many clinically significant Gram-negative organisms.

Antimicrobial Activity

Amikacin has been shown to be active against the following bacteria, both *in vitro* and in clinical infections (see **INDICATIONS AND USAGE**).

Gram-positive Bacteria

Staphylococcus species

Gram-negative Bacteria

Pseudomonas species

Escherichia coli

Proteus species (indole-positive and indole-negative)

Klebsiella species

Enterobacter species

Serratia species

Acinetobacter species

Amikacin has demonstrated *in vitro* activity against the following bacteria. The safety and effectiveness of amikacin in treating clinical infections due to these bacteria have not been established in adequate and well-controlled trials.

Citrobacter freundii

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide cumulative results of the *in vitro* susceptibility tests for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized test method.[1, 3] Standardized procedures are based on a dilution method (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of amikacin powder. The MIC values should be interpreted according to the criteria provided in Table 1.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure requires the use of standardized inoculum concentrations and paper disks impregnated with 30 mcg of amikacin.[2, 3] The disk diffusion values should be interpreted according to the criteria provided in Table 1.

Table 1: Susceptibility Test Interpretive Criteria for Amikacin

Pathogen	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion Zone Diameters (mm)		
	S	I	R	S	I	R
Enterobacteriaceae[*]	≤ 16	32	≥ 64	≥ 17	15 to 16	≤ 14
Pseudomonas aeruginosa	≤ 16	32	≥ 64	≥ 17	15 to 16	≤ 14
Acinetobacter spp.	≤ 16	32	≥ 64	≥ 17	15 to 16	≤ 14

other Non-*Enterobacteriaceae*	≤ 16	32	≥ 64	-	-	-
Staphylococcus spp.†	≤ 16	32	≥ 64	≥ 17	15 to 16	≤ 14

S = susceptible, I = intermediate, R = resistant

* For *Salmonella* and *Shigella* spp., aminoglycosides may appear active *in vitro* but are not effective clinically; the results should not be reported as susceptible

† For *staphylococci* that test susceptible, aminoglycosides are used only in combination with other active agents that test susceptible

A report of “Susceptible” indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentration at the infection site necessary to inhibit growth of the pathogen. A report of “Intermediate” indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of “Resistant” indicates that the antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentrations usually achievable at the infection site; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test.[1, 2, 3] Standard amikacin powder should provide the following range of MIC values provided in Table 2. For the diffusion technique using the 30-mcg amikacin disk the criteria provided in Table 2 should be achieved.

Table 2: Acceptable Quality Control Ranges for Amikacin

Quality Control Organism	Minimum Inhibitory Concentrations (mcg/mL)	Disk Diffusion Zone Diameters (mm)
Escherichia coli ATCC 25922	0.5 to 4	19 to 26
Pseudomonas aeruginosa ATCC 27853	1 to 4	18 to 26
Staphylococcus aureus ATCC 25923	Not Applicable	20 to 26
Staphylococcus aureus ATCC 29213	1 to 4	Not Applicable
Enterococcus faecalis ATCC 29212	64 to 256	Not Applicable

INDICATIONS AND USAGE

Amikacin sulfate injection USP is indicated in the short-term treatment of serious infections due to susceptible strains of Gram-negative bacteria, including *Pseudomonas* species, *Escherichia coli*, species of indole-positive and indole-negative *Proteus*, *Providencia* species, *Klebsiella-Enterobacter-Serratia*

species and *Acinetobacter* (*Mima-Herellea*) species.

Clinical studies have shown amikacin sulfate injection USP to be effective in bacterial septicemia (including neonatal sepsis); in serious infections of the respiratory tract, bones and joints, central nervous system (including meningitis) and skin and soft tissue; intra-abdominal infections (including peritonitis); and in burns and postoperative infections (including postvascular surgery). Clinical studies have shown amikacin also to be effective in serious complicated and recurrent urinary tract infections due to these organisms. Aminoglycosides, including amikacin sulfate injection USP, are not indicated in uncomplicated initial episodes of urinary tract infections unless the causative organisms are not susceptible to antibiotics having less potential toxicity.

Bacteriologic studies should be performed to identify causative organisms and their susceptibilities to amikacin. Amikacin may be considered as initial therapy in suspected gram-negative infections, and therapy may be instituted before obtaining the results of susceptibility testing. Clinical trials demonstrated that amikacin was effective in infections caused by gentamicin- and/or tobramycin-resistant strains of gram-negative organisms, particularly *Proteus rettgeri, Providencia stuartii, Serratia marcescens* and *Pseudomonas aeruginosa*. The decision to continue therapy with the drug should be based on results of the susceptibility tests, the severity of the infection, the response of the patient and the important additional considerations contained in the **WARNINGS box** above.

Amikacin has also been shown to be effective in staphylococcal infections and may be considered as initial therapy under certain conditions in the treatment of known or suspected staphylococcal disease such as, severe infections where the causative organism may be either a gram-negative bacterium or a staphylococcus, infections due to susceptible strains of staphylococci in patients allergic to other antibiotics, and in mixed staphylococcal/gram-negative infections.

In certain severe infections such as neonatal sepsis, concomitant therapy with a penicillin-type drug may be indicated because of the possibility of infections due to gram-positive organisms such as streptococci or pneumococci.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of amikacin sulfate injection USP and other antibacterial drugs, amikacin sulfate injection USP should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

A history of hypersensitivity to amikacin is a contraindication for its use. A history of hypersensitivity or serious toxic reactions to aminoglycosides may contraindicate the use of any other aminoglycoside because of the known cross-sensitivities of patients to drugs in this class.

WARNINGS

See **WARNINGS box** above.

Aminoglycosides can cause fetal harm when administered to a pregnant woman. Aminoglycosides cross the placenta and there have been several reports of total irreversible, bilateral congenital deafness in children whose mothers received streptomycin during pregnancy. Although serious side effects to the fetus or newborns have not been reported in the treatment of pregnant women with other aminoglycosides, the potential for harm exists. Reproduction studies of amikacin have been performed in rats and mice and revealed no evidence of impaired fertility or harm to the fetus due to amikacin. There are no well-controlled studies in pregnant women, but investigational experience does not include any positive evidence of adverse effects to the fetus. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential

hazard to the fetus.

Contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than non-asthmatic people.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including amikacin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary since CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

PRECAUTIONS

General

Prescribing amikacin sulfate injection in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Aminoglycosides are quickly and almost totally absorbed when they are applied topically, except to the urinary bladder, in association with surgical procedures. Irreversible deafness, renal failure and death due to neuromuscular blockade have been reported following irrigation of both small and large surgical fields with an aminoglycoside preparation.

Amikacin sulfate injection is potentially nephrotoxic, ototoxic and neurotoxic. The concurrent or serial use of other ototoxic or nephrotoxic agents should be avoided either systemically or topically because of the potential for additive effects. Increased nephrotoxicity has been reported following concomitant parenteral administration of aminoglycosides, antibiotics and cephalosporins. Concomitant cephalosporins may spuriously elevate creatinine determinations.

Since amikacin is present in high concentrations in the renal excretory system, patients should be well-hydrated to minimize chemical irritation of the renal tubules. Kidney function should be assessed by the usual methods prior to starting therapy and daily during the course of treatment.

If signs of renal irritation appear (casts, white or red cells or albumin), hydration should be increased. A reduction in dosage (see **DOSAGE AND ADMINISTRATION**) may be desirable if other evidence of renal dysfunction occurs such as decreased creatinine clearance; decreased urine specific gravity; increased BUN, creatinine or oliguria. If azotemia increases or if a progressive decrease in urinary output occurs, treatment should be stopped.

Note: When patients are well hydrated and kidney function is normal, the risk of nephrotoxic reactions with amikacin is low if the dosage recommendations (see DOSAGE AND ADMINISTRATION) are not exceeded.

Elderly patients may have reduced renal function which may not be evident in routine screening tests such as BUN or serum creatinine. A creatinine clearance determination may be more useful. Monitoring of renal function during treatment with aminoglycosides is particularly important.

Aminoglycosides should be used with caution in patients with muscular disorders such as myasthenia

gravis or parkinsonism since these drugs may aggravate muscle weakness because of their potential curare-like effect on the neuromuscular junction.

In vitro mixing of aminoglycosides with beta-lactam antibiotics (penicillin or cephalosporins) may result in a significant mutual inactivation. A reduction in serum half-life or serum level may occur when an aminoglycoside or penicillin-type drug is administered by separate routes. Inactivation of the aminoglycoside is clinically significant only in patients with severely impaired renal function. Inactivation may continue in specimens of body fluids collected for assay, resulting in inaccurate aminoglycoside readings. Such specimens should be properly handled (assayed promptly, frozen or treated with beta-lactamase).

Cross-allergenicity among aminoglycosides has been demonstrated.

As with other antibiotics, the use of amikacin may result in overgrowth of non-susceptible organisms. If this occurs, appropriate therapy should be instituted.

Aminoglycosides should not be given concurrently with potent diuretics (see **WARNINGS box**).

Information for Patients

Patients should be counseled that antibacterial drugs including amikacin sulfate injection should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When amikacin sulfate injection is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by amikacin sulfate injection or other antibacterial drugs in the future.

Patients should be counseled that diarrhea is a common problem caused by antibiotics, and it usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as 2 or more months after having taken their last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term studies in animals to evaluate carcinogenic potential have not been performed, and mutagenicity has not been studied. Amikacin administered subcutaneously to rats at doses up to 4 times the human daily dose did not impair male or female fertility.

Pregnancy

Teratogenic Effects

Category D (see **WARNINGS** section).

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from amikacin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Aminoglycosides should be used with caution in premature and neonatal infants because of the renal immaturity of these patients and the resulting prolongation of serum half-life of these drugs.

ADVERSE REACTIONS

All aminoglycosides have the potential to induce auditory, vestibular and renal toxicity and neuromuscular blockade (see **WARNINGS box**). They occur more frequently in patients with present or past history of renal impairment, of treatment with other ototoxic or nephrotoxic drugs and in patients treated for longer periods and/or with higher doses than recommended.

Neurotoxicity-Ototoxicity

Toxic effects on the eighth cranial nerve can result in hearing loss, loss of balance, or both. Amikacin primarily affects auditory function. Cochlear damage includes high frequency deafness and usually occurs before clinical hearing loss can be detected.

Neurotoxicity-Neuromuscular Blockade

Acute muscular paralysis and apnea can occur following treatment with aminoglycoside drugs.

Nephrotoxicity

Elevation of serum creatinine, albuminuria, presence of red and white cells, casts, azotemia, and oliguria have been reported. Renal function changes are usually reversible when the drug is discontinued. As would be expected with any aminoglycoside, reports of toxic nephropathy and acute renal failure have been received during postmarketing surveillance.

Other

In addition to those described above, other adverse reactions which have been reported on rare occasions are skin rash, drug fever, headache, paresthesia, tremor, nausea and vomiting, eosinophilia, arthralgia, anemia, hypotension and hypomagnesemia. Macular infarction sometimes leading to permanent loss of vision has been reported following intravitreous administration (injection into the eye) of amikacin.

OVERDOSAGE

In the event of overdosage or toxic reaction, peritoneal dialysis or hemodialysis will aid in the removal of amikacin from the blood. In the newborn infant, exchange transfusion may also be considered.

DOSAGE AND ADMINISTRATION

The patient’s pretreatment body weight should be obtained for calculation of correct dosage. Amikacin sulfate injection may be given intramuscularly or intravenously.

The status of renal function should be estimated by measurement of the serum creatinine concentration or calculation of the endogenous creatinine clearance rate. The blood urea nitrogen (BUN) is much less reliable for this purpose. Reassessment of renal function should be made periodically during therapy.

Whenever possible, amikacin concentrations in serum should be measured to assure adequate but not excessive levels. It is desirable to measure both peak and trough serum concentrations intermittently during therapy. Peak concentrations (30 to 90 minutes after injection) above 35 mcg/mL and trough concentrations (just prior to the next dose) above 10 mcg/mL should be avoided. Dosage should be adjusted as indicated.

Intramuscular Administration for Patients with Normal Renal Function

The recommended dosage for adults, children and older infants (see **WARNINGS box**) with normal renal function is 15 mg/kg/day divided into 2 or 3 equal doses administered at equally divided intervals, i.e., 7.5 mg/kg q12h or 5 mg/kg q8h. Treatment of patients in the heavier weight classes should not exceed 1.5 grams/day.

When amikacin is indicated in newborns (see **WARNINGS box**), it is recommended that a loading dose of 10 mg/kg be administered initially to be followed with 7.5 mg/kg every 12 hours.

The usual duration of treatment is 7 to 10 days. It is desirable to limit the duration of treatment to short-term whenever feasible. The total daily dose by all routes of administration should not exceed 15 mg/kg/day. In difficult and complicated infections where treatment beyond 10 days is considered, the use of amikacin should be reevaluated. If continued, amikacin serum levels and renal, auditory and vestibular functions should be monitored. At the recommended dosage level, uncomplicated infections due to amikacin-sensitive organisms should respond in 24 to 48 hours. If definite clinical response does not occur within 3 to 5 days, therapy should be stopped and the antibiotic susceptibility pattern of the invading organism should be rechecked. Failure of the infection to respond may be due to resistance of the organism or to the presence of septic foci requiring surgical drainage.

When amikacin is indicated in uncomplicated urinary tract infections, a dose of 250 mg twice daily may be used.

DOSAGE GUIDELINES
ADULTS AND CHILDREN WITH NORMAL RENAL FUNCTION

Patient Weight		Dosage		
lbs	**kg**	**7.5 mg/kg q12h**	**OR**	**5 mg/kg q8h**
99	45	337.5 mg		225 mg
110	50	375 mg		250 mg
121	55	412.5 mg		275 mg
132	60	450 mg		300 mg
143	65	487.5 mg		325 mg
154	70	525 mg		350 mg
165	75	562.5 mg		375 mg
176	80	600 mg		400 mg
187	85	637.5 mg		425 mg
198	90	675 mg		450 mg
209	95	712.5 mg		475 mg
220	100	750 mg		500 mg

Intramuscular Administration for Patients with Impaired Renal Function

Whenever possible, serum amikacin concentrations should be monitored by appropriate assay procedures. Doses may be adjusted in patients with impaired renal function either by administering normal doses at prolonged intervals or by administering reduced doses at a fixed interval.

Both methods are based on the patient's creatinine clearance or serum creatinine values since these have been found to correlate with aminoglycoside half-lives in patients with diminished renal function. These dosage schedules must be used in conjunction with careful clinical and laboratory observations of the patient and should be modified as necessary. Neither method should be used when dialysis is being performed.

Normal Dosage at Prolonged Intervals

If the creatinine clearance rate is not available and the patient's condition is stable, a dosage interval in hours for the normal dose can be calculated by multiplying the patient's serum creatinine by 9, e.g., if the serum creatinine concentration is 2 mg/100 mL, the recommended single dose (7.5 mg/kg) should be administered every 18 hours.

Reduced Dosage at Fixed Time Intervals

When renal function is impaired and it is desirable to administer amikacin at a fixed time interval, dosage must be reduced. In these patients, serum amikacin concentrations should be measured to assure accurate administration of amikacin and to avoid concentrations above 35 mcg/mL. If serum assay determinations are not available and the patient's condition is stable, serum creatinine and creatinine clearance values are the most readily available indicators of the degree of renal impairment to use as a guide for dosage.

First, initiate therapy by administering a normal dose, 7.5 mg/kg, as a loading dose. This loading dose is the same as the normally recommended dose which would be calculated for a patient with a normal renal function as described above.

To determine the size of maintenance doses administered every 12 hours, the loading dose should be reduced in proportion to the reduction in the patient's creatinine clearance rate:

$$\text{Maintenance Dose Every 12 hours} = \frac{\text{observed CC in mL/min}}{\text{normal CC in mL/min}} \times \text{calculated loading dose in mg}$$

(CC—creatinine clearance rate)

An alternate rough guide for determining reduced dosage at 12 hour intervals (for patients whose steady state serum creatinine values are known) is to divide the normally recommended dose by the patient's serum creatinine.

The above dosage schedules are not intended to be rigid recommendations but are provided as guides to dosage when the measurement of amikacin serum levels is not feasible.

Intravenous Administration

The individual dose, the total daily dose, and the total cumulative dose of amikacin sulfate are identical to the dose recommended for intramuscular administration. The solution for intravenous use is prepared by adding the contents of a 500 mg vial to 100 or 200 mL of sterile diluent such as 0.9% sodium chloride injection or 5% dextrose injection or any other compatible solutions listed below.

The solution is administered to adults over a 30 to 60 minute period. The total daily dose should not exceed 15 mg/kg/day and may be divided into either 2 or 3 equally-divided doses at equally-divided intervals.

In pediatric patients, the amount of fluid used will depend on the amount of amikacin sulfate ordered for the patient. It should be a sufficient amount to infuse the amikacin over a 30 to 60 minute period. Infants should receive a 1 to 2 hour infusion.

Amikacin should not be physically premixed with other drugs but should be administered separately according to the recommended dose and route.

Stability in IV Fluids

Amikacin sulfate is stable for 24 hours at room temperature at concentrations of 0.25 and 5 mg/mL in the following solutions:

5% Dextrose Injection USP

5% Dextrose USP and 0.2% Sodium Chloride Injection USP

5% Dextrose USP and 0.45% Sodium Chloride Injection USP

0.9% Sodium Chloride Injection USP

Lactated Ringer's Injection USP

Normosol® M in 5% Dextrose Injection USP

(or Plasma-Lyte 56 injection in 5% Dextrose USP in water).

Normosol® R in 5% Dextrose Injection USP
(or Plasma-Lyte 148 injection in 5% Dextrose USP in water).

In the above solutions with amikacin sulfate concentrations of 0.25 and 5 mg/mL, solutions aged for 60 days at 4°C and then stored at 25°C had utility times of 24 hours.

At the same concentrations, solutions frozen and aged for 30 days at -15°C, thawed, and stored at 25°C had utility times of 24 hours.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Aminoglycosides administered by any of the above routes should not be physically premixed with other drugs but should be administered separately.

Because of the potential toxicity of aminoglycosides, “fixed dosage” recommendations which are not based upon body weight are not advised. Rather, it is essential to calculate the dosage to fit the needs of each patient.

HOW SUPPLIED

Amikacin Sulfate Injection USP is supplied as a colorless solution which requires no refrigeration. At times the solution may become a very pale yellow; this does not indicate a decrease in potency.

Amikacin Sulfate Injection USP is supplied as follows:

NDC Number	Strength
0703-9032-93	500 mg per 2 mL
0703-9040-93	1 gram per 4 mL

2 mL and 4 mL vials are packaged in shelf packs of 10.

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN

REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI). *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard - Tenth Edition*. CLSI document M07-A10, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.

2. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Disk Diffusion Susceptibility Tests; Approved Standard – Twelfth Edition.* CLSI document M02-A12, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.

3. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-fifth Informational Supplement.* CLSI document M100-S25. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.

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Táncsics M. út 82 Hungary
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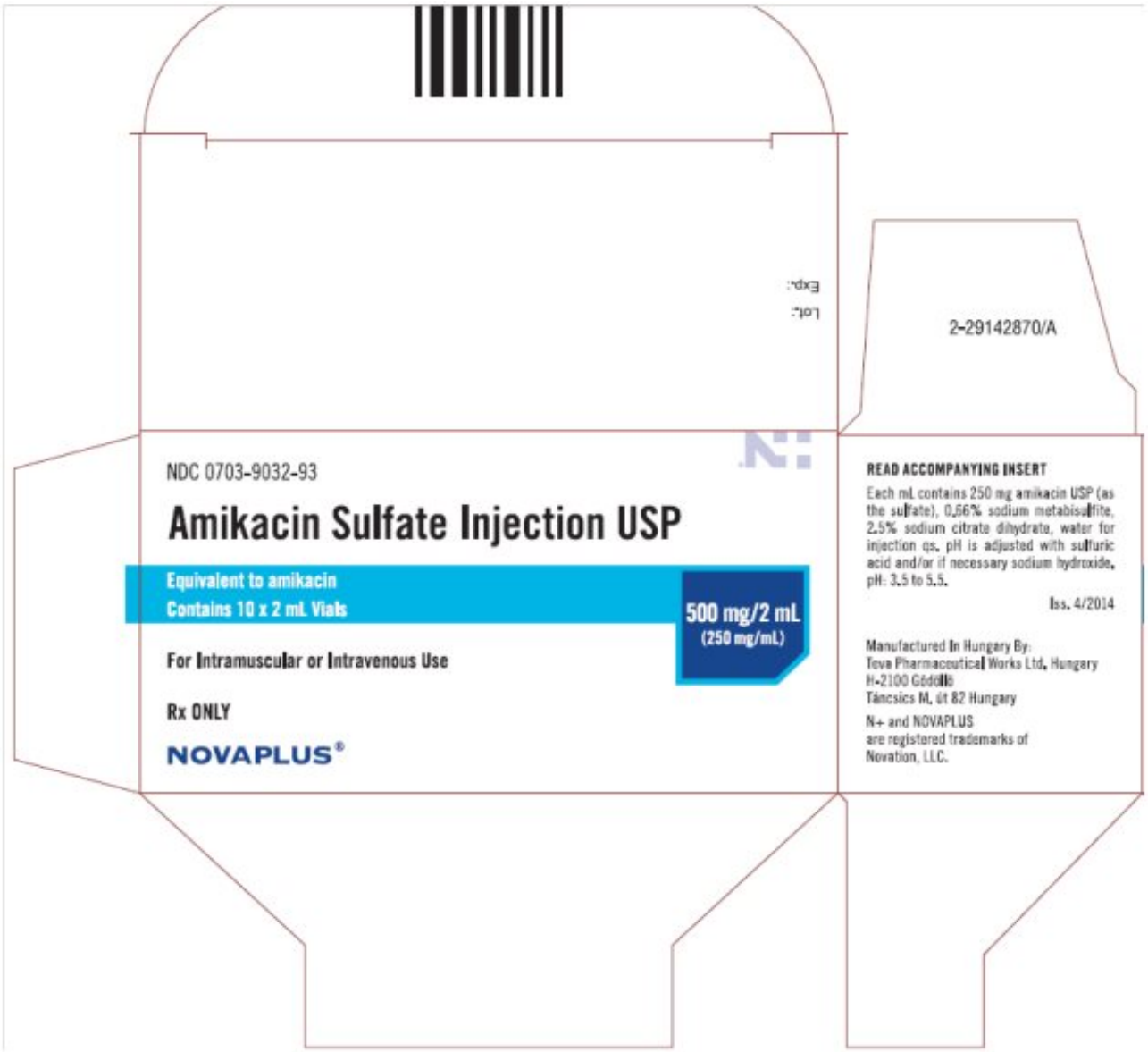
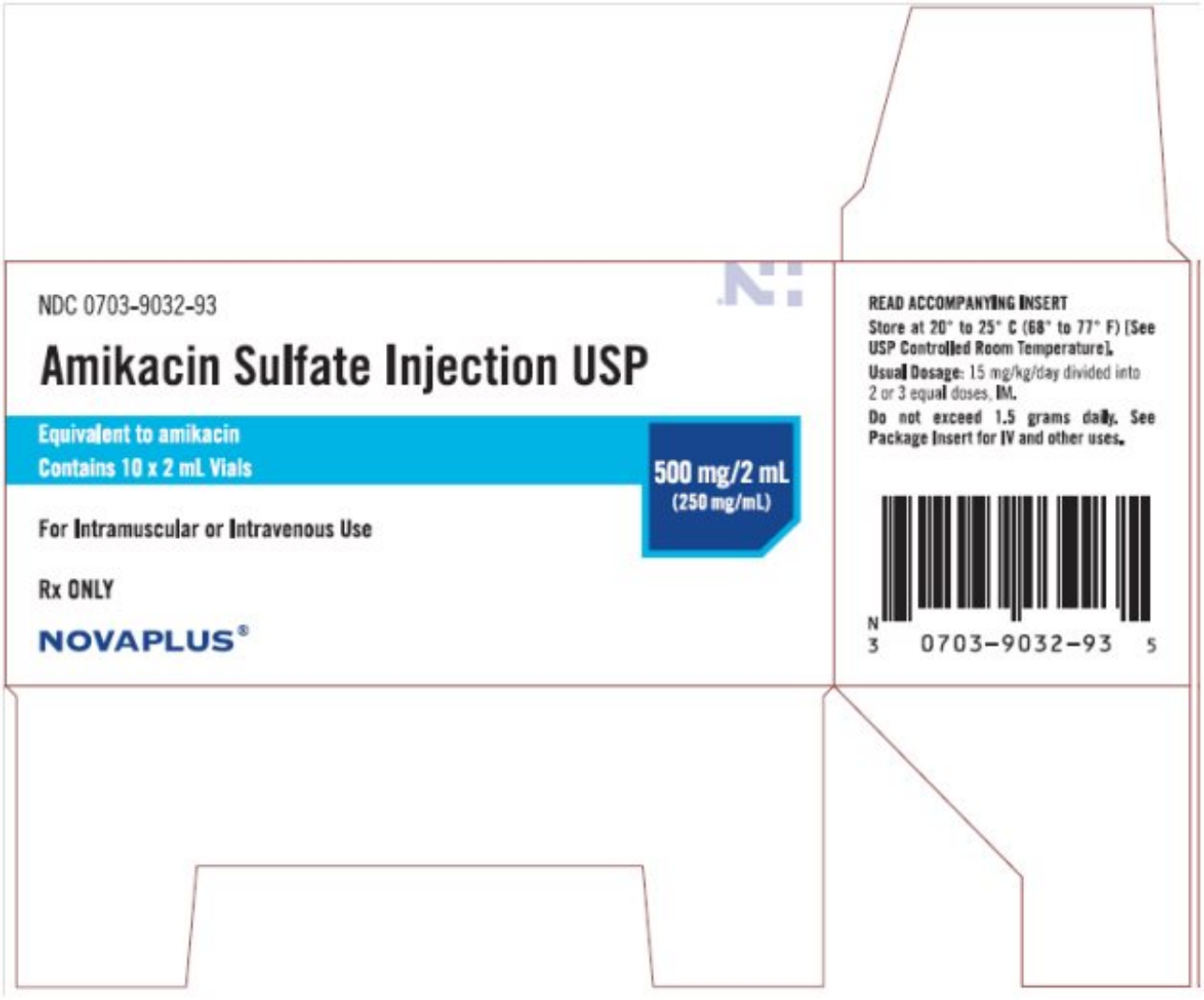
Rev. A 7/2015

Package/Label Display Panel, Part 1 of 2



Package/Label Display Panel, Part 2 of 2



Amikacin Sulfate Injection USP 500 mg/2 mL Vial, 10 x 2 mL Carton Text

NDC 0703-9032-93

Amikacin Sulfate Injection USP

Equivalent to amikacin

Contains 10 x 2 mL Vials

500 mg/2 mL

(250mg/mL)

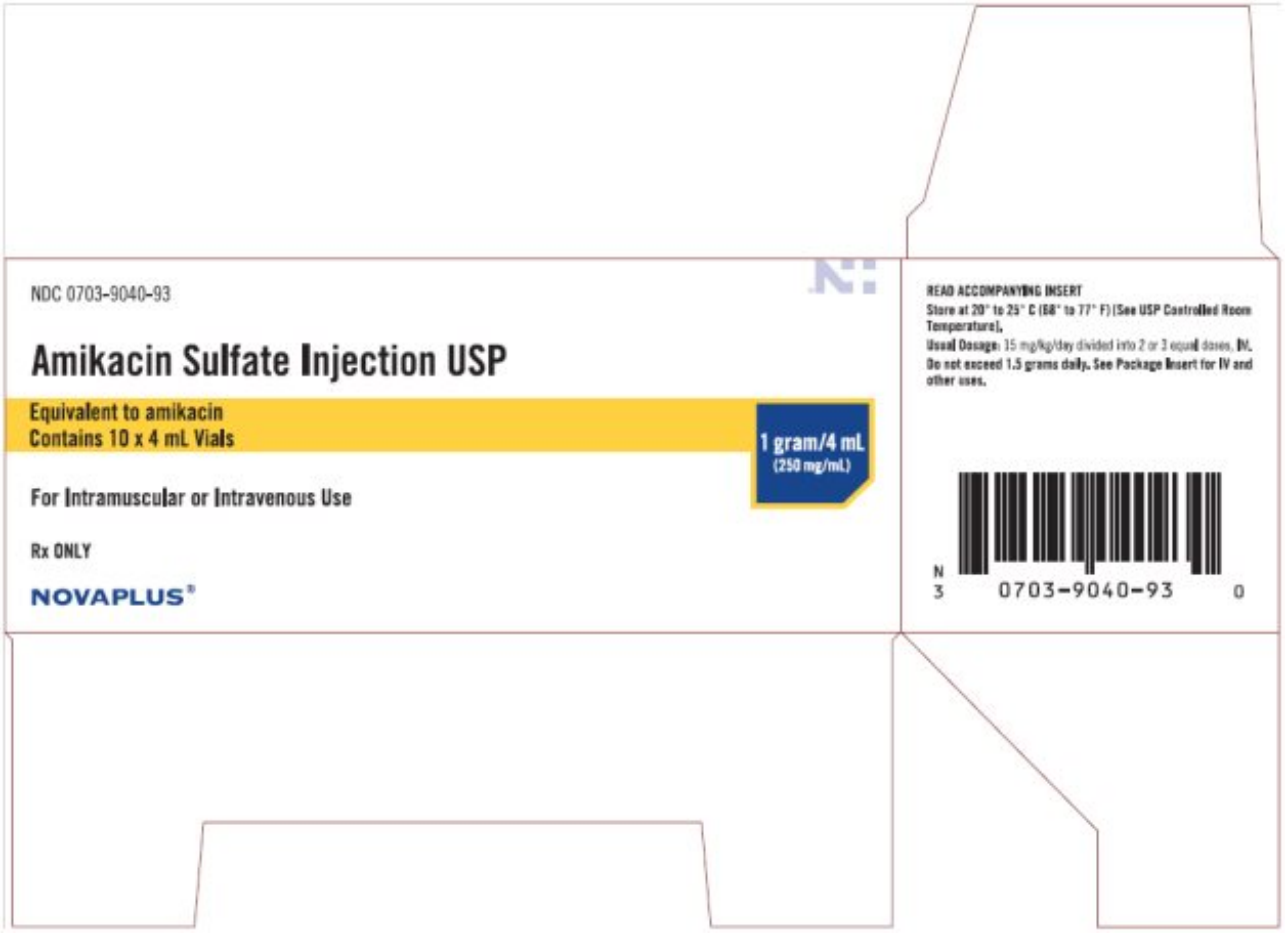
For Intramuscular or Intravenous Use

Rx ONLY

NOVAPLUS®

Package/Label Display Panel, Part 1 of 2

Package/Label Display Panel, Part 2 of 2



Amikacin Sulfate Injection USP 1 gram/4 mL Vial, 10 x 4 mL Carton Text

NDC 0703-9040-93

Amikacin Sulfate Injection USP

Equivalent to amikacin

Contains 10 x 4 mL Vials

1 gram/4 mL

(250mg/mL)

For Intramuscular or Intravenous Use

Rx ONLY

NOVAPLUS®

AMIKACIN SULFATE

amikacin sulfate injection, solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0703-9032
Route of Administration	INTRAVENOUS, INTRAMUSCULAR	**DEA Schedule**	

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
AMIKACIN SULFATE (UNII: N6M33094FD) (AMIKACIN - UNII:84319SGC3C)	AMIKACIN	500 mg in 2 mL

Inactive Ingredients	
Ingredient Name	**Strength**
TRISODIUM CITRATE DIHYDRATE (UNII: B22547B95K)	
SODIUM METABISULFITE (UNII: 4VON5FNS3C)	
WATER (UNII: 059QF0KO0R)	
SULFURIC ACID (UNII: O40UQP6WCF)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0703-9032-93	10 in 1 CARTON	11/26/2014	
1	NDC:0703-9032-91	2 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA064045	11/26/2014	

AMIKACIN SULFATE

amikacin sulfate injection, solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0703-9040
Route of Administration	INTRAVENOUS, INTRAMUSCULAR	**DEA Schedule**	

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
AMIKACIN SULFATE (UNII: N6M33094FD) (AMIKACIN - UNII:84319SGC3C)	AMIKACIN	1 g in 4 mL

Inactive Ingredients	
Ingredient Name	**Strength**
TRISODIUM CITRATE DIHYDRATE (UNII: B22547B95K)	
SODIUM METABISULFITE (UNII: 4VON5FNS3C)	
WATER (UNII: 059QF0KO0R)	

SULFURIC ACID (UNII: O40UQP6WCF)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0703-9040-93	10 in 1 CARTON	11/26/2014	
1	NDC:0703-9040-91	4 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA064045	11/26/2014	

Labeler - Teva Parenteral Medicines, Inc. (794362533)

Revised: 9/2015 Teva Parenteral Medicines, Inc.